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EXAMINER	
DESAI, ANAND U	
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1656	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/06/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/506,367	HEMBERGER ET AL.	
	Examiner	Art Unit	
	Anand U. Desai, Ph.D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *January 3, 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-79* is/are pending in the application.

4a) Of the above claim(s) *56-73* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-55 and 74-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20051003; 20070103*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, claims 37-55, and 74-79, drawn to a hydroxyaklyl starch protein conjugate in the reply filed on December 15, 2006 is acknowledged. The species election of a hydroxyalkly starch having a molecular weight of 130 kDa, a degree of substitution of 0.5, and the protein interferon alpha is acknowledged.

2. Claims 56-73 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on December 15, 2006.

Priority

3. Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). Receipt is acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. The priority date is March 6, 2002.

Information Disclosure Statement

4. The information disclosure statements (IDSs) submitted on October 3, 2005, and January 3, 2007 are being considered by the examiner.

Specification

5. The disclosure is objected to because of the following informalities:

6. The molecular mass should be abbreviated as kDa rather than kD throughout the specification.

7. Applicant is reminded of the proper language and format for an abstract of the disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 150 words. It is important that the abstract not exceed 150 words in length since the space provided for the abstract on the computer tape used by the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

The last sentence of the abstract uses legal phraseology, "...the use of said conjugates and compositions...". Suggest, "...the use of the conjugates and compositions...".

Appropriate correction is required.

Claim Objections

8. Claims 44-47 are objected to because of the following informalities: the molecular mass should be abbreviated, kDa rather than kD. Appropriate correction is required.

Double Patenting

9. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or

improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

10. Claims 37, 41, 42, 44, 45, 48-53, 55, 74, 78, and 79 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, and 6-11 of U.S. Patent No. 6,083,909 (10/3/2005 IDS document AB). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the instant patent application that are drawn to a protein hydroxyalkyl starch conjugate comprises the species of the issued patent that is claiming a hemoglobin hydroxyethyl starch conjugate. The conjugate is linked by selective amide bonds between free amino groups of the hemoglobin and the oxidized form of hydroxyethyl starch. The hydroxyethyl starch has an average molecular weight 1 to 40 kDa. The hydroxyethyl starch has a molar degree of substitution of 0.1 to 0.8 and a ratio of C_2:C_6 substitution in the range from 2 to 20, based on hydroxyethyl groups (see claims 1, and 6-11).

11. Claims 37, 39, 41-55, 74-76, 78, and 79 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 86, and 87 of copending Application No. 10/472,002 (US 2005/0063943 A1). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of both applications are drawn to hydroxyalkyl starch protein conjugates. The claims of the copending application claim a conjugate of hydroxyalkyl starch with at least one active ingredient and the pharmaceutical composition comprising the conjugate. The active ingredient is disclosed as any protein, oligopeptide or polypeptide. The active ingredient can be bound to a linker. The average molecular weight of the hydroxyethyl starch is from 1 to 300 kDa. The hydroxyethyl starch has a molar degree of substitution of 0.1 to 0.8 and a ratio of 2 to 20 for the ratio of C_2:C_6 substitution, based on hydroxyethyl groups (see claims 76, 81, 83, 85, 86 and 87).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

12. Claims 37-39, 41-53, 55, 74-76, 78, and 79 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 37-50, 54, 56, and 74-78 of copending Application No. 10/506,366 (US 2006/0217293 A1). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application are drawn to a conjugate of a hydroxyalkyl starch and a low molecular weight substance. The low molecular weight substance is reasonably interpreted to encompass the species claimed in the instant patent application, because examples 13 (page 7, [0074]) and 29 (page 9, [0092]) describe the conjugation of lueteinizing hormone-releasing

hormone and glucagon, respectively. The claims of the copending application describe the hydroxyethyl starch with an average molecular weight of about 130 kDa. The degree of substitution from about 0.3 to 0.7, and a ratio of substitution of 8 to 12 for C_2:C_6 substitution, based on hydroxyethyl groups (see particularly claims 37, 44-47, and 56).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

13. Claims 37-39, 41-43, 50-55, 74-76, and 79 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 5-8, 21, and 22 of copending Application No. 10/567,265. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application are drawn to a conjugate comprising hydroxyalkyl starch and a protein. The claims are drawn to a pharmaceutical composition comprising the conjugate (see claims 5-8, 21, and 22).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

14. Claims 37-55, and 74-79 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 5, 8, 12, 15-18, 44, 45, 47-53, 55, 56, 58-61 and 81-85 of copending Application No. 11/078,582 (US 2006/0019877 A1). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application are drawn to a conjugate comprising hydroxyalkyl starch and a protein. The claims are drawn to a pharmaceutical composition

comprising the conjugate. The hydroxyethyl starch average molecular weight is from 1 to 300 kDa. The molar degree of substitution is from 0.1 to 0.8, and a ratio of C_2:C_6 substitution in the range from 2 to 20, based on hydroxyethyl groups. The claims of the corresponding application are also drawn to a modified erythropoietin, wherein a cysteine amino acid residue is added to the modified erythropoietin (see claims 1, 2, 5, 8, 12, 15-18, 44, 45, 47-53, 55, 56, 58-61, and 81-85).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

15. Claims 37-39, 41-55, 74-76, 78, and 79 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 34-50 of copending Application No. 11/078,098 (US 2005/0238723 A1). Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application are drawn to a hydroxyalkyl starch polypeptide conjugate. The claims are also drawn to a pharmaceutical composition comprising the conjugate (see particularly claims 34, 39, 40, and 41).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

16. Claims 37-55, and 74-79 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 25-36, and 38-59 of copending Application No. 11/518,352. Although the conflicting claims are not identical, they

are not patentably distinct from each other because the claims of the copending application are drawn to a conjugate comprising a protein and a hydroxyalkyl starch. The claims are also drawn to a pharmaceutical composition comprising the conjugate (see claims 25-36, and 38-59).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

17. Claims 37-55, and 74-79 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 13-22, and 24-31 of copending Application No. 11/530,264. Although the conflicting claims are not identical, they are not patentably distinct from each other because the claims of the copending application are drawn to a conjugate comprising hydroxyalkyl starch and a protein. The claims are drawn to a pharmaceutical composition comprising the conjugate. The hydroxyethyl starch average molecular weight is from 1 to 300 kDa. The molar degree of substitution is from 0.1 to 0.8 (see claims 13-22, and 24-31).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

18. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

19. Claims 37-55, and 74-79 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

20. In claims 37 and 74, it is unclear how is the conjugate is "based on" a covalent bond? The vague language is confusing. Can a conjugate be other than a covalent bond?

21. At the end of claim 37, the bonding resulting in the coupling reaction can be modified by a further reaction. It is unclear what "appropriate might be"? How can it be modified? Unclear since the covalent bond is not specified above, how this alters the limitation on it?

Suggest for claim 37, A hydroxyalkystarch-protein conjugate, wherein the bond between the hydroxyalkylstarch and the protein is a covalent bond, which is the result of a coupling reaction between (i) the terminal aldehyde group...(ii)a functional group of the protein...

22. In claims 40 and 77, it is unclear if the functional group is introduced by recombinant techniques or if the amino acid sequence is recombinantly modified and then the functional group reacts with the modified amino acid sequence. Unclear what "original" is?

23. In claims 48, and 49, it is unclear what the hydroxyalkyl starch is being substituted with. What is the hydroxyalkyl starch substituted with?

Claim Rejections - 35 USC § 112, First Paragraph, Written Description

24. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

25. Claims 37-55, and 74-79 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are rejected under 35 U.S.C. 112, 1st paragraph, Written Description, because the specification does not disclose a representative number of species of functional groups derived by a chemical reaction with the aldehyde group of a hydroxyalkyl starch polysaccharide, and a representative number of hydroxyalkyl starch polysaccharides that can be conjugated to any protein, which would lead one skilled in the art to conclude that applicant was in possession of the claimed invention. The claims are also rejected under 35 U.S.C. 112, 1st paragraph, Written Description, because the specification does not disclose functional derivatives or fragments of the protein.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, Paragraph 1, "Written Description" Requirement, published at Federal Register, Vol. 66, No. 4, pp. 1099-1111 outline the method of analysis of claims to determine whether adequate written description is present. The first step is to determine what the claim as a whole covers, i.e., discussion of the full scope of the claim. Second, the application should be fully reviewed to understand how applicant provides support for the claimed invention including each element and/or step, i.e., compare the scope of the claim with the scope of the description. Third, determine whether the applicant was in possession of the claimed invention as a whole at the time of filing. This should include the following considerations: (1) actual reduction to practice,

(2) disclosure of drawings or structural chemical formulas, (3) sufficient relevant identifying characteristics such as complete structure, partial structure, physical and/or chemical properties and functional characteristics when coupled with a known or disclosed correlation between function and structure, (4) method of making the claimed invention, (5) level of skill and knowledge in the art and (6) predictability of the art. For each claim drawn to a single embodiment or species, each of these factors is to be considered with regard to that embodiment or species. For each claim drawn to a genus, each of these factors is to be considered to determine whether there is disclosure of a representative number of species that would lead one skilled in the art to conclude that applicant was in possession of the claimed invention. Where skill and knowledge in the art is high adequate written description would require fewer species to be disclosed than in an art where little is known; further, more species would need to be disclosed to provide adequate written description for a highly variable genus.

First, what do the claims as a whole cover? The claims are drawn to a hydroxyalkyl starch protein conjugate. The conjugate is produced based on the covalent binding of a terminal aldehyde group or a functional group derived from this aldehyde group by a chemical reaction present on the hydroxyalkyl starch polysaccharide, with a functional group on the protein that is able to react with the aldehyde or a functional group derived from this aldehyde by a chemical reaction. The claims disclose the functional group derived by the chemical reaction is one of the functional groups of a bifunctional linker molecule. The claims disclose the functional group on the protein can also be a bifunctional linker molecule. The functional group on the protein can be introduced into the protein by recombinant modification of the original amino acid sequence. The covalent bond between the hydroxyaklyl starch and the protein can be an amide or amine

bond. The hydroxyalkystarch polysaccharide can have a molecular weight range from about 4 to about 1000 kDa, a degree of substitution of about 0.3 to about 0.7, and a ratio of C_2 to C_6 substitutions from 8 to 12. Dependent claims 51 and 52 disclose the protein only by functional characteristics.

Second, how does the scope of the claims compare to the scope of the disclosure? The scope of the claim is broader than the scope of the disclosure. The disclosure describes the selective oxidation of hydroxyalkyl species, hydroxyethyl starch (both low and high molecular weight forms) and the conjugation of the oxidized hydroxyethyl starch with full-length proteins. The disclosure does not describe the conjugation of other hydroxyalkyl species or the conjugation of derivatives or fragments of proteins.

Third, the factors need to be considered.

(1) What was actually reduced to practice?

The method of conjugating oxidized hydroxyethyl starch with amine containing proteins was reduced to practice (see examples 1 to 17).

(2) Is there disclosure of drawings or structural chemical formulas?

There is a general disclosure of cross-linking agents, but no general structure is provided for each moiety, each moiety is defined by what portion of the hydroxyalkyl starch molecule interacts with what portion of the amino acid sequence of the protein. There is no disclosure of how any particular structure gives rise to the function.

(3) Are there sufficient relevant identifying characteristics disclosed?

The functional characteristics of the proteins are disclosed but they are not coupled with a known or disclosed correlation between function and structure. The specification does not

disclose the structure of bifunctional linkers with a representative number of hydroxyalkyl starch molecules, or bifunctional linkers with functional derivatives or fragments of the protein that retain the function of the original protein once conjugated.

(4) Is there at least one method of making the claimed invention disclosed?

Hydroxyethyl starch conjugated to amine containing full-length proteins using cross-linker ethyldimethylaminopropylcarbodiimide is disclosed.

(5) What is the level of skill in the art and what knowledge is present in the art? / (6) What is the level of predictability of the art?

The level of skill in the art of polymer protein conjugation and elucidation of information from the structure is high, about that of a PhD scientist with several years' experience.

Maout et al. (1/3/2007 IDS document 221) discuss the unpredictability in outcome of a proteins function after conjugation with a hydroxyethyl starch polysaccharide. The hydroxyethyl starch was conjugated to hemoglobin using the carboxylate functional group derived by reacting hydroxyethyl starch with benzene 1,2,4,5-tetracarboxylic anhydride (see page 133, Figure 1, and page 139, Experimental section). The HES-BTC-hemoglobin conjugate is not effective as a blood substitute (see page 138, Conclusion section). Therefore, it is not predictable that any functional group can be used to conjugate any hydroxyalkyl starch with any protein.

The level of predictability in this art is very low since, until the structure to function correlation is examined, there is no information upon which to base a prediction of what molecule might be suitable as functional group for conjugating a hydroxyalkyl starch with any protein.

Thus, having analyzed the claims with regard to the Written Description guidelines, it is clear that the specification does not disclose a representative number of species which would lead one skilled in the art to conclude that applicant was in possession of the claimed invention.

Claim Rejections - 35 USC § 112, 1st paragraph, enablement rejection

26. Claims 37-55 and 74-79 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for hydroxyethyl starch protein conjugates disclosed in the examples, using ethyldimethylaminopropylcarbodiimide to conjugate the amine containing proteins recited, does not reasonably provide enablement for any hydroxyalkyl starch protein conjugate. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are rejected because of undue experimentation to make and use the claimed hydroxyalkyl starch protein conjugate. The undue experimentation arises due to the unpredictability based on the different unknown structures of materials, such as the genus of hydroxyalklyl starch polysaccharides, the functional groups on the hydroxyalkyl starch polysaccharide, the functional group on the protein that are being used to conjugate the polysaccharide with the protein.

In *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) eight factors should be addressed in determining enablement.

While the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection. The language should focus on those factors, reasons,

and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims. This can be done by making specific findings of fact, supported by the evidence, and then drawing conclusions based on these findings of fact. For example, doubt may arise about enablement because information is missing about one or more essential parts or relationships between parts which one skilled in the art could not develop without undue experimentation. In such a case, the examiner should specifically identify what information is missing and why one skilled in the art could not supply the information without undue experimentation. See MPEP § 2164.06(a). References should be supplied if possible to support a prima facie case of lack of enablement, but are not always required. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). However, specific technical reasons are always required.

1) The nature of the invention: the instant claims are directed to a hydroxyalkyl starch protein conjugate. The conjugate is produced based on the covalent binding of a terminal aldehyde group or a functional group derived from this aldehyde group by a chemical reaction present on the hydroxyalkyl starch polysaccharide, with a functional group on the protein that is able to react with the aldehyde or a functional group derived from this aldehyde by a chemical reaction. The claims disclose the functional group derived by the chemical reaction is one of the functional groups of a bifunctional linker molecule. The claims disclose the functional group on the protein can also be a bifunctional linker molecule. The functional group on the protein can be introduced into the protein by recombinant modification of the original amino acid sequence.

The covalent bond between the hydroxyaklyl starch and the protein can be an amide or amine bond. The hydroxyalkyl starch polysaccharide can have a molecular weight range from about 4 to about 1000 kDa, a degree of substitution of about 0.3 to about 0.7, and a ratio of C_2 to C_6 substitutions from 8 to 12.

3) The predictability or unpredictability of the art: & 6) The quantity of experimentation necessary: & 7.) The state of the prior art: the prior art has shown a large quantity of experimentation is often necessary to overcome the unpredictable nature of protein conjugation with polysaccharides, including hydroxyalkyl starch polysaccharides.

The art has demonstrated that structural modifications affect the functional outcome of protein conjugates. Maout et al. (1/3/2007 IDS document 221) discuss the unpredictability in outcome of a proteins function after conjugation with a hydroxyethyl starch polysaccharide. The hydroxyethyl starch was conjugated to hemoglobin using the carboxylate functional group derived by reacting hydroxyethyl starch with benzene 1,2,4,5-tetracarboxylic anhydride (see page 133, Figure 1, and page 139, Experimental section). The HES-BTC-hemoglobin conjugate is not effective as a blood substitute (see page 138, Conclusion section). Therefore, it is not predictable that any functional group can be used to conjugate any hydroxyalkyl starch with any protein.

The level of predictability in this art is very low, and there is no information upon which to base a prediction of what molecule might be suitable as a functional group that can form a covalent bond between any hydroxyalkyl starch and any protein.

Therefore, the unpredictability arises due to the different structural effects of bifunctional linkers on the protein conjugate. Consequently, there would be a large quantity of

experimentation necessary to determine what bifunctional linkers have the structural features required to produce a functional hydroxyalkyl starch protein conjugate.

How would one of skilled in the art know how to make and use any hydroxyalkyl starch protein conjugate if the functional effects are unpredictable?

8.) Level of skill in the art: the level of skill in this art is high, at least that of a doctoral scientist with several years of experience in the art.

In consideration of the Wands factors, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching, and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

Claim Rejections - 35 USC § 102

27. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

28. Claims 37, 41, 42, 44, 45, 48-53, 55, 74, 78, and 79 are rejected under 35 U.S.C. 102(e) as being anticipated by Sommermeyer et al. (U.S. Patent 6,083,909; 10/3/2005 IDS document AB).

Sommermeyer et al. describe a hemoglobin hydroxyethyl starch conjugate. The conjugate is linked by selective amide bonds between free amino groups of the hemoglobin and the oxidized form of hydroxyethyl starch. The hyrdoxyethyl starch is oxidized selectively using oxidizing agent, 0.1 N iodine solution, on the terminal aldehyde of the hydroxyethyl starch (see last sentence of Abstract, and col. 8, beginning on line 53, example A.1). The hydroxyethyl starch has an average molecular weight 1 to 40 kDa. The hydroxyethyl starch has a molar degree of substitution of 0.1 to 0.8 and a ratio of C_2:C_6 substitution in the range from 2 to 20, based on hydroxyethyl groups (see col. 8, line 50 – col. 9, line 55, and claims 1, 6-11). The hemoglobin hydroxyethyl starch conjugate can be used to treat mammals in need of oxygen (see claim 27).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

29. Claims 37, 41, 42, 44-48, 50-53, 55, 74, and 79 are rejected under 35 U.S.C. 102(b) as being anticipated by Cerny (U.S. Patent 4,900,780).

Cerny describes an acellular resuscitative fluid comprising hemoglobin conjugated to hydroxyethyl starch. The hemoglobin is converted to an oxyacid or diketone form, which reacts with the aldehyde form of the hydroxyethyl starch polymer (see col. 2, line 42-49). The covalent bond results in an amide linkage between the hemoglobin and hydroxyethylstarch molecules.

The hydroxyethyl starch can range from 60 to 450 kDa. About 50 kDa in claim 45 is reasonably interpreted to be encompassed by the range disclosed. The starch is substituted to a degree of from 0.2 to 0.9 by hydroxyethylation (see col. 1, line 67 - col. 2, line 2). Hemoglobin transports oxygen and is therefore a transport protein.

The acellular resuscitative fluid can be freeze-dried, and then reconstituted with 0.9% NaCl solution containing 80 mg/ 100% nicotinamide adenine dinucleotide (NADH), and nicotinamide dinucleotide phosphate (NADPH) at 80 mg/ 100% for administration in vivo (see col. 8, example 18, and particularly claims 1-6).

30. Claims 37, 38, 41, 42, 50-53, 55, 74, 75, and 79 are rejected under 35 U.S.C. 102(b) as being anticipated by Beez et al. (Translated version of German Patent Application 26 16 086; 1/3/2007 IDS document 46).

Beez et al. describe the conjugation of hydroxyethyl starch with stroma-free hemoglobin using a chemical cross-linking agent, bromine cyanide (see page 6, reaction example). The conjugate is characterized by having an amide bond between the terminal aldehyde of the hydroxyethyl starch and hemoglobin (see page 7, picture of conjugate). Claim 39 and 76 are not rejected, because the hemoglobin molecule does not comprise a bifunctional linker molecule coupled to the hemoglobin, rather the amine group on hemoglobin reacts with the cross-linking agent on the hydroxyethyl starch. The conjugate is used to as a colloidal volume substitute, which has oxygen transport function based on the hemoglobin molecule. The conjugate has a longer residence time in the body (see page 8, 1st paragraph).

Conclusion

31. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anand U. Desai, Ph.D. whose telephone number is (571) 272-0947. The examiner can normally be reached on Monday - Friday 9:00 a.m. - 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Kathleen Kerr Bragdon can be reached on (517) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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